May 4, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

CITIZEN PETITION

The undersigned, on behalf of Medeva Pharmaceuticals, Inc. (Medeva), submits this petition pursuant to sections 505 and 508 of the Federal Food, Drug, and Cosmetic Act (FDC Act) and 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs not approve any abbreviated new drug applications (ANDAs) for generic versions of Zaroxolyn® Tablets (metolazone tablets, USP) or Mykrox® Tablets (metolazone tablets, USP) or any new drug applications (NDAs) for other metolazone products until the established name for Zaroxolyn® Tablets has been changed from "metolazone tablets, USP" to "metolazone slow-low release tablets" either by designation of "metolazone slow-low release tablets" as an official name by the Food and Drug Administration (FDA) or by the addition of a "metolazone slow-low release tablets" monograph to the *United States Pharmacopeia* (*USP*).

A. ACTION REQUESTED

Medeva requests the following actions from the Commissioner of Food and Drugs:

(1) that FDA change the established name for Zaroxolyn® Tablets from "metolazone, tablets, USP" to "metolazone slow-low release tablets" either by initiating a rulemaking pursuant to section 508 of the FDC Act to designate "metolazone slow-low release tablets" as the new official name for Zaroxolyn® Tablets, or by officially requesting the USP Nomenclature Committee and the United States Adopted Names (USAN) Council to add a "metolazone slow-low release tablets" monograph to the *USP*; and

(2) that FDA not approve any ANDAs for Zaroxolyn® Tablets or Mykrox® Tablets which may be pending or filed in the future or any NDAs for other metolazone products until the established name for Zaroxolyn® Tablets has been changed from "metolazone tablets, USP" to "metolazone slow-low release tablets."

B. STATEMENT OF GROUNDS

I. Introduction

Medeva currently markets two metolazone tablets products that have been approved by the FDA: Zaroxolyn® Tablets and Mykrox® Tablets. FDA approved an NDA for Zaroxolyn® Tablets on November 27, 1973 in which the metolazone is supplied in 2.5 mg, 5 mg, and 10 mg tablets.[1] Zaroxolyn® Tablets is indicated for the

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[1] The labeling for Zaroxolyn® Tablets states that the product is available in tablets containing either 2 ½, 5, or 10 mg of metolazone. However, the *Approved Drug Products with Therapeutic Equivalence* (hereinafter "*Orange Book*") uses a decimal dosing reference for the Zaroxolyn® Tablets (i.e., 2.5 mg, 5 mg, 10 mg).

treatment of salt and water retention, including edema accompanying congestive heart failure and renal diseases, and for the treatment of hypertension. A new tablet formulation of metolazone with increased bioavailability was studied. After two adequate and well-controlled studies were performed on this tablet formulation of metolazone, a second NDA was submitted for metolazone with the tradename Microx.[2] FDA approved this NDA for Mykrox® Tablets on October 30, 1987. Mykrox® Tablets is supplied in .5 mg tablets[3] and is indicated for the treatment of hypertension. Due to the increased bioavailability of metolazone in Mykrox® Tablets, Zaroxolyn® Tablets and Mykrox® Tablets are not bioequivalent, and therefore not therapeutically equivalent, and may not be interchanged. In fact, the approval for Mykrox® Tablets required a warning against interchangeability with Zaroxolyn® Tablets (or products bioequivalent to Zaroxolyn® Tablets) to be placed at the very beginning of the package insert for Mykrox® Tablets. This warning states in bold print:

Orange Book, CDER, FDA, at 3-228 (19th Ed. 1999).

2 The Summary Basis of Approval (SBA) for this metolazone product has the tradename Microx rather than Mykrox®. FDA approved a supplement changing the spelling of the tradename to Mykrox® on September 20, 1988.

3 The labeling for Mykrox® Tablets states that the tablets contain ½ mg of metolazone. However, as with the Zaroxolyn® Tablets, the *Orange Book* uses a decimal dosing reference for Mykrox® Tablets (i.e., 0.5 mg). *Orange Book* at 3-228. While the Orange Book refers to Mykrox ® Tablets as 0.5 mg, it is not unreasonable that physicians may omit the zero in front of the decimal point when prescribing .5 mg metolazone tablets, USP.

DO NOT INTERCHANGE

MYKROX TABLETS ARE A RAPIDLY AVAILABLE FORMULATION OF METOLAZONE FOR ORAL ADMINISTRATION. MYKROX TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS MORE RAPID AND COMPLETE BIOAVAILABILITY ARE NOT THERAPEUTICALLY EQUIVALENT TO ZAROXOLYN® TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS SLOW AND INCOMPLETE BIOAVAILABILITY. FORMULATIONS BIOEQUIVALENT TO MYKROX AND FORMULATIONS BIOEQUIVALENT TO ZAROXOLYN SHOULD NOT BE INTERCHANGED FOR ONE ANOTHER.[4]

At the same time that the Mykrox ® Tablets received approval, FDA required a similar warning to be placed in bold print in the Zaroxolyn® Tablets package insert. This warning states:

DO NOT INTERCHANGE

DO NOT INTERCHANGE ZAROXOLYN TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS SLOW AND INCOMPLETE BIOAVAILABILITY AND ARE NOT THERAPEUTICALLY EQUIVALENT AT THE SAME DOSES TO MYKROX® TABLETS, A MORE RAPIDLY AVAILABLE AND COMPLETELY BIOAVAILABLE METOLAZONE PRODUCT. FORUMULATIONS BIOEQUIVALENT TO ZAROXOLYN AND FORUMULATIONS BIOEQUIVALENT TO MYKROX SHOULD NOT BE INTERCHANGED FOR ONE ANOTHER.[5]

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4 Mykrox® Tablets Package Insert.

5 Zaroxolyn® Tablets Package Insert.

Other than Zaroxolyn® Tablets and Mykrox® Tablets, there are currently no metolazone products approved in the United States.

Because Zaroxolyn® Tablets and Mykrox® Tablets are not interchangeable, the current practice with respect to prescribing metolazone products is that doctors generally prescribe the products by tradename rather than by established or generic name. This practice avoids confusion or misinterpretation that might occur, for example, between 5.0 mg Zaroxolyn® Tablets (written as 5.0 mg metolazone tablets) and .5 mg Mykrox® Tablets (written as .5 mg metolazone tablets).[6] This practice will, of course, change when generic metolazone products enter the marketplace and prescriptions are regularly written with only the generic name.

The recent attention that has been paid to medical errors, including medication errors, however, suggests that this potential for confusion is a significant problem and should be addressed at this juncture before FDA approves other metolazone products.

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6 A review of the adverse drug experience files at Medeva did not reveal a single reported instance of Mykrox® Tablets being inadvertently dispensed in place of Zaroxolyn® Tablets, or the converse.

II. Medical Errors

Medical errors, including medication errors, have recently come to the forefront as a significant problem.[7] These medication errors can result from confusion that may arise when the names of drugs are too similar. This can be a problem for both tradenames and nonproprietary names. For example, a pharmacist may be easily confused by a prescription for metolazone tablets .5 mg and fill it with the 5 mg product or vice versa. A physician might include on the prescription a mark that appears to be a decimal point but in reality is nothing more than an inadvertent drag of the pen. It is not unreasonable that this type of error could occur more than occasionally.

FDA seeks to limit this potential for confusion with respect to tradenames prior to approval by referring tradenames to the Office of Postmarketing Drug Risk Assessment (OPDRA)[8] for examination of similarity to other names as part of the NDA review process. This approach serves to attempt to identify names that might pose problems before the drugs actually enter the marketplace and have the opportunity to be confused with drugs with similar names. A recent example of drug name confusion surrounding a

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7 See IOM Report, To Err Is Human: Building a Safer Health System (2000); FDA, Minimizing Medical Product Errors: A Systems Approach (Jan. 8, 1998).

8 Until recently this task was handled by the Labeling and Nomenclature Committee (LNC). However, FDA has recently begun referring tradenames to OPDRA for review.

tradename is Celebrex®. The manufacturer of Celebrex® changed the drug's name from Celebra because of FDA's concern that Celebra could be confused with Celexa™.

The process for selecting nonproprietary names also aims to protect patients from medication errors based on confusing or similar names. However, the naming process is not perfect, and nonproprietary names may need to be changed at some point after they have been selected. For example, the similarity between the nonproprietary names of two cardiac drugs, amrinone and amiodarone, has resulted in 11 medication errors, including one death. In response to these errors, the USP Nomenclature Committee and the USAN Council[9] have approved changing the nonproprietary name and the current official monograph title of amrinone to inamrinone.[10]

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9 The USAN Council is comprised of members of the three organizations that sponsor the USAN program (the American Medical Association, the American Pharmaceutical Association, and the USP) as well as a liaison representative of the FDA. *USP Dictionary of USAN and International Drug Names* (35th ed. 1998), at 6.

10 Amrinone Becomes Inamrinone, USP Quality Review, No. 73 (Mar. 2000). This name change is scheduled to become effective July 1, 2000. In September of 1999, the USP Nomenclature Committee and the USAN Council jointly recommended changing amrinone to inamrinone and amiodarone to camiodarone. Pharmacopeial Forum 25(5) (Sept.-Oct. 1999). The USP Medication Errors Reporting Program disseminated a practitioner survey in order to obtain reaction and comment to the proposed name change. In response to the results of the practitioner survey, the USP Nomenclature Committee decided to approve the change for amrinone to inamrinone, but to postpone the recommendation for changing amiodarone to camiodarone. Pharmacopeial Forum 26(2) (Mar.-Apr. 2000).

III. Naming Process

The FDC Act requires the label of a drug to bear the established name of the drug to the exclusion of any other nonproprietary name.[11] The established name of the drug is defined as

> (A) the applicable official name designated pursuant to 358 of this title [i.e., § 508 of the FDC Act], or (B), if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium, or (C) if neither clause (A) nor clause (B) of this subparagraph applies, then the common or usual name, if any, of such drug or of such ingredient....[12]

Section 508(a) of the FDC Act authorizes FDA to designate an official name for any drug if FDA determines "that such action is necessary or desirable in the interest of usefulness and simplicity."[13] When FDA determines after review of an official name identified in an official compendium that such official name is "unduly complex or is not useful for any other reason," FDA will request from the compendium a recommendation of a single official name for such drug that will have usefulness and simplicity.[14] If FDA determines that the recommended name is useful, FDA will designate that name as the official

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11 21 U.S.C. § 352(e)(1)(A)(i).

12 Id. § 352(e)(3).

13 Id. § 358(a).

14 Id. § 358(b), (c). Section 201(j) of the FDC Act defines an official compendium as either the *USP*, the *Homeopathic Pharmacopeia of the United States*, or the *National Formulary*, or any supplement to any of them. Id. § 321(j).

name.[15] If FDA determines that such recommended name is not useful, FDA will designate a single official name for the drug that FDA determines is useful.[16] Any designation of an official name by FDA shall be made in accordance with notice-and-comment rulemaking.[17]

Under the statutory approach, the established name for a drug will come from one of three sources. If FDA designates an official name in accordance with section 508 of the FDC Act, that name is the established name for the drug. If FDA does not designate an official name, the established name for a drug is its compendial name. The compendial name for a drug is the title of a monograph published in the *USP* or the *NF*.[18] If no compendial name exists, then the established name is the common or usual name of the drug. The common or usual name for a drug is generally the USAN (i.e., the name adopted by the USAN Council). If there is a USP monograph, the USAN is generally used as the title of the monograph, resulting in a compendial name that is the same as the USAN. As discussed below, a USAN is often chosen with the expectation that it will be

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15 Id. § 358(c).

16 Id.

17 Id.

18 For purposes of section 502(e)(3) of the FDC Act, "an article is considered to be recognized in an official compendium if it has the 'identity' prescribed for a drug in the compendium." FDA, Response to Novartis Citizen Petition, Docket No. 96P-0459, at 16 (Nov. 2, 1998)(citing 21 C.F.R. § 299.5(a) and (b)).

suitable for use as the title of the monograph should the article be recognized in the *USP* or the *NF*.[19]

FDA does not routinely designate official names for drug products under section 508 of the FDC Act.[20] Even though FDA has decided it will not routinely designate official names under section 508 of the FDC Act, FDA will continue to publish official names pursuant to section 508 of the FDC Act when the agency determines that "[t]he USAN or other official or common or usual name is unduly complex or is not useful for any other reason."[21]

The role of an established name is to "facilitate[] communication by providing a common designation for identical drugs, or combinations of drugs, available from several sources."[22] The USAN program is directed at producing simple and useful

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19 *USP Dictionary of USAN and International Drug Names* at 6.

20 21 C.F.R. § 299.4(e). In the absence of designation by FDA of an official name, interested persons may rely on as the established name, the current compendial name or the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names*. Id. The *USAN and the USP Dictionary of Drug Names* is no longer published and has been incorporated in the *USP Dictionary of USAN and International Drug Names*. *USP Dictionary of USAN and International Drug Names* at 5.

21 21 C.F.R. § 299.4(e)(1).

22 Ingredient Name, FDA, CDER Data Standards Manual, No. C-DRG-00401 (Apr. 12, 1994).

nonproprietary names for drugs that may be used by the public at large without the restrictions that trademarks may impose.[23] A proposal for a USAN generally originates from a firm or an individual early in the development process and is expected to conform to established "Guiding Principles for Coining U.S. Adopted Names for Drugs" and to be reasonably free from conflict with other names.[24] In many cases, the USAN will be the title of the USP monograph that includes the identity for the product. In fact, the USAN Council chooses a name with the expectation that it will be suitable for use as the title of the monograph should the drug be recognized in the *USP* or *NF*.[25]

IV. Name Change for Metolazone

The established name for both Zaroxolyn® Tablets and Mykrox® Tablets is "metolazone tablets, USP." FDA has not designated an official name for metolazone pursuant to section 508 of the FDC Act. A monograph for metolazone tablets has been

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23 *USP Dictionary of USAN and International Drug Names* at 6.

24 Id. at 7.

25 Id. at 6. The responsibilities of the USAN Council and the USP Nomenclature Committee do not completely overlap however. The USP Nomenclature Committee deals with several areas not within the scope of the USAN Council, including terminology for dosage-form monograph titles. Id. The USP Nomenclature Committee is also responsible for "coining suitable [monograph] titles where such are needed because of the lack of public (nonproprietary) names or to improve the names already in use. The titles shall be in harmony with convenience in prescribing and with accepted tenets of general usage and shall be simple, useful, and clearly distinguishing and differentiating." Id. (emphasis added).

established and published in the *USP*.[26] As discussed above, Zaroxolyn® Tablets and Mykrox® Tablets are not bioequivalent and may not be interchanged. The importance of the difference in formulation between Zaroxolyn® Tablets and Mykrox® Tablets is stressed in the package inserts of both products through the use of bolded warnings in two sections of the package inserts of each product. Moreover, the package insert for Mykrox® Tablets states in bold that

> SINCE A SAFE AND EFFECTIVE DIURETIC DOSE HAS NOT BEEN ESTABLISHED, MYKROX TABLETS SHOULD NOT BE USED WHEN DIURESIS IS DESIRED.[27]

Clearly, FDA already recognizes the potential safety issues that might ensue from the use of one product in place of the other. Because of the more rapid and greater bioavailability of Mykrox® Tablets, there is a potential for overdosage if the two products cannot be distinguished.

Results from a study designed to compare the diuretic action of Mykrox® Tablets (.5 mg) and Zaroxolyn® Tablets (2.5 mg) show that the diuretic action of Mykrox® Tablets is at least five times greater than that of Zaroxolyn® Tablets within the first four hours of dosing.[28] Overdosage can result in orthostatic hypotension, dizziness,

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26 *USP* 24 (2000) at 1100.

27 Mykrox® Tablets Package Insert.

28 Miller RP, et al., Comparison of three formulations of metolazone: bioavailability

drowsiness, syncope, electrolyte abnormalities, hemoconcentration, and hemodynamic changes due to plasma volume depletion.[29] At high doses, lethargy may progress to coma within a few hours.[30] All of these effects of overdosage can be serious, especially in elderly patients who are likely to be taking several concomitant medications. Conversely, substitution of one formulation for the other could lead to under dosing, an event that could mean a patient would not receive the desired therapeutic benefit and would therefore suffer the consequences of untreated disease. Both of these possible outcomes can be avoided by granting the requested relief.

Furthermore, because Zaroxolyn® Tablets are available in a 5 mg tablet and a Mykrox® Tablet is .5 mg, there would be a definite potential for confusion or errors in the prescribing and dispensing of these products if the established name remains the same for both products and a generic product is approved for either innovator product. Therefore, because the current compendial name is not useful for differentiating Zaroxolyn® Tablets from Mykrox® Tablets, Medeva requests that FDA initiate a notice-and-comment rulemaking in accordance with its authority to establish an official name under section 508 of the FDC Act. Alternatively, Medeva requests that FDA work with

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and pharmacological effects. Curr. Ther. Res. 1988; 43(6):1133-1142.

29 Mykrox® Tablets Package Insert; Zaroxolyn® Tablets Package Insert.

30 Id.

the USP Nomenclature Committee and the USAN Council to add a new monograph with the title "metolazone slow-low release tablets." In either case, Medeva requests that FDA not approve any ANDAs or NDAs for metolazone products until the established name for Zaroxolyn® Tablets has been changed to "metolazone slow-low release tablets."

There is precedent for different USP monographs for different formulations of the same product. For example, the *USP* contains monographs for two different phenytoin sodium capsules formulations – "extended phenytoin sodium capsules" and "prompt phenytoin sodium capsules."[31] Similarly, there are different USP monographs for "griseofulvin tablets" and "ultramicrosize griseofulvin tablets."[32]

The name change requested by Medeva does not conflict with the position FDA has taken regarding the dispute over FDA's approval of SangCya® as a generic version of the Novartis cyclosporine product Neoral®. In that case FDA was concerned that Novartis was trying to insulate Neoral® from generic competition with the narrow modifier "for microemulsion" that might not be applicable to other potential innovative bioequivalent formulations.[33] Here, however, the name proposed by Medeva expresses a

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31 *USP* 24 (2000) at 1325-26.

32 Id. at 790-91.

33 FDA, Response to Citizen Petition, Docket No. 96P-0459, at 16 (Nov. 2, 1998).

characteristic of the formulation that would be related to whether another product is bioequivalent to it. A generic version of Zaroxolyn® Tablets would necessarily have to be less rapidly and less completely bioavailable than Mykrox® Tablets in order to be considered bioequivalent to Zaroxolyn® Tablets. Therefore, the addition to the *USP* of the monograph with a modifier for this metolazone product does not raise the same concerns that the "cyclosporine oral solution for microemulsion" raises.

Moreover, it is prudent to make this change at this juncture before any other metolazone products are approved. Making this change now can only serve to protect patients from potential medication errors, but without waiting for the medication errors to actually occur. Because there are no other metolazone products approved at this time, no interests are harmed by this precautionary measure.

V. Conclusion

Medeva requests that due to the potential for confusion regarding generic prescribing of metolazone products, no other metolazone products be approved until the established name for Zaroxolyn® Tablets is changed from "metolazone tablets, USP" to "metolazone slow-low release tablets." Medeva further requests that FDA initiate a rulemaking to designate "metolazone slow-low release tablets" as the official name for Zaroxolyn® Tablets in accordance with section 508 of the FDC Act, or officially request

the USP Nomenclature Committee and the USAN Council to add a new monograph for "metolazone slow-low release tablets" to the *USP*.

C. ENVIRONMENTAL IMPACT

The actions herein requested are subject to categorical exclusion under 21 C.F.R. § 25.31.

D. ECONOMIC IMPACT

An economic impact statement will be submitted at the request of the Commissioner.

E. CERTIFICATION STATEMENT

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies,

and that it includes representative data and information to the petitioner which are unfavorable to the petition.

Respectfully Submitted,

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